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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,671	05/03/2006	**Julian Bonnerjea**	2006-0763	4399

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EXAMINER	
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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,671	BONNERJEA ET AL.	
	Examiner	Art Unit	
	David A. Saunders	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/13/08* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 1-22 are pending.

RESPONSE TO ELECTION/RESTRICTION

Applicant's election without traverse of Group II (Claims 13-22) in the reply filed on 3/3/09 is acknowledged. It is noted that Group II should have included only claims 13-14 and 21-22, since claim 15 depends from claim 12 of Group I.

In any event, the claims of both Groups I and II are under consideration.

OBJECTION(S) TO DISCLOSURE

The amendment filed 5/3/06 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The incorporation by reference of Prov. Applic. Ser. No. 60/608,104 is improper, since it was not stated in the specification at the International Stage.

Applicant is required to cancel the new matter in the reply to this Office Action.

OBJECTION(S) TO CLAIMS

Claims 13 and 17-20 are objected to because of the following informalities: Appropriate correction is required.

In claim 13, line 3, "monomelic" should be –monomeric--.

In claims 17-20 all recitations of "pi" should be –pI--.

REJECTION(S) UNDER 35 USC 112, SECOND PARAGRAPH

Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has variously referred to "the ion exchange material", "the ion exchanger material" and "the ion exchanger". Consistent terminology is required in claim 1 and all dependent claims.

In claim 5, "the chromatographic support material" lacks antecedent basis.

In claim 12, "the protease inhibitor" lacks antecedent basis.

In claim 13, part 1 refers to an "ion exchange material" while part 2 refers to "the ion exchanger". Claims 18 and 21 refer to "the ion exchange material" while claim 16 refers to "the ion exchanger". Consistent terminology is required throughout the claims.

All recitations of "preferably in claims 1, 8, 11, 13, 14 and 19-21 are indefinite.

REJECTION(S) UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 8-13, 15-16 and 21-22 are rejected under 35 U.S.C. 102(e) as being anticpated by Bonnerjea et al (WO 2004/076485, cited in IDS of 1/4/07).

Bonnerjea et al ('485) is properly cited since it has an International filing date that pre-dates any of applicant's priority applications, it is published in English, and it designates the US.

Bonnerjea et al shows step 1 of instant claim 1, in which an antibody is purified on Protein A. Bonnerjea et al shows step 2 of instant claim 1, in which the antibody is then applied to an anion exchange chromatography column and recovered in the flow-through, while contaminating protein A binds to the anion exchange material.

Bonnerjea et al shows step 3 of instant claim 1, in which the antibody recovered from the flow-through is applied to a cation exchange chromatography column. Monomeric antibody and aggregates are both adsorbed to the cation exchange chromatography column and then differentially eluted from therefrom. This separation of the Monomeric antibody and aggregates by cation exchange chromatography is considered to correspond to "fractionating the flow-through" as recited in step 3 of instant claim 1.

The rejection is based upon a broad interpretation of what is meant by "fractionating the flow-through". It is believed that applicant considers that "fractionating the flow-through" should mean that the flow-through is fractionated as it exits the anion exchange chromatography column, e.g. by collecting the flow-through in multiple fractions, rather than as a single flow through fraction.

However, the Office considers that applicant's disclosure has not explicitly thus narrowed the meaning of "fractionating the flow-through". There is no explicit definition of "fractionating the flow-through" that limits it to only a collecting of the flow-through in multiple fractions, rather than as a single flow through fraction. Nothing in the disclosure precludes the term "fractionating" as also encompassing a further fractionating of a single flow-through peak by an additional method, such as the cation exchange chromatography step of Bonnerjea et al ('485). In fact, the only point in applicant's disclosure where "fractionating" per se is discussed is in para. [0039] of the disclosure, as published in US 2008/0312425 (cited on PTO-892). Therein applicant states that "Preferably, fractionation is achieved by fractionating or splitting the antibody peak of the flow-through into at least two fractions and a wasting tail fraction." Since applicant has prefaced this teaching with "Preferably", nothing in para. [0039] rules out the term "fractionating" as also encompassing a further fractionating of a single flow-through peak by an additional method, such as the cation exchange chromatography (as in Bonnerjea et al ('485)), or "gel permeation or size exclusion chromatography" (as taught by applicant in para. [0039]).

For these reasons instant claim 1 is considered anticipated. Bonnerjea et al ('485) teaches the recombinant protein A that has been engineered to have a single

point of attachment, as in instant dependent claims 2-5 (p 4). Bonnerjea et al ('485) teaches the degree of purification achieved by anion exchange chromatography, as recited in instant claim 6 (p 6). Bonnerjea et al ('485) teaches the types of antibodies and the cell cultures of instant claims 8-10 (pp 6-7). Bonnerjea et al ('485) teaches the lack of treatment by protease inhibitors, as in instant claim 11 (p 7). Bonnerjea et al ('485) teaches the protease inhibitors of instant claim 12 (pp 7-8). Regarding claim 15, Bonnerjea et al ('485) teaches that the monomeric antibody is recovered in a "first" peak fraction and the aggregates come off in a "second" tailing fraction during elution from the cation exchanger (p 33). Bonnerjea et al ('485) teaches the buffer conditions for anion exchange chromatography recited in instant claim 16 (pp 9-10).

Independent claim 13 s also anticipated by Bonnerjea et al ('485). In this case step 1 of claim 13 corresponds to the anion exchange chromatography step of Bonnerjea et al ('485), and step 2 of claim 13 corresponds to the cation exchange chromatography step of Bonnerjea et al ('485). Again, the term "fractionating" is broadly interpreted as encompassing a further fractionating of a single flow-through peak from the anion exchanger by an additional method, such as the cation exchange chromatography of Bonnerjea et al ('485). Regarding dependent claim 21, Bonnerjea et al ('485) teaches the percent flow through recovery instantly recited is obtained from the anion exchanger. Regarding dependent claim 22, Bonnerjea et al ('485) teaches that the monomeric antibody is recovered in a "first" peak fraction and the aggregates come off in a "second" tailing fraction during elution from the cation exchanger.

REJECTION(S) UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8-13 And 21 are rejected under 35 U.S.C. 103(a) as being obvious over JP 7-155194 A (cited on PTO-892) in view of Racher et al (Manufacture of Therapeutic Antibodies, 1999, cited on PTO-892) and, as necessary, EP 0,284,268 (cited on PTO-892).

For purposes of examination, the Office will refer to the AIPN JPO machine translation (attached to the JP 7-155194 A document). This action will refer to the translation as '194 and will note portions thereof by the para. nos. in square brackets. Document '194 teaches the purification of the monoclonal antibody produced by hybridoma V3beta1F4 (any hybridoma is inherently a mammalian cell line) according to the following steps of the Example.

Step 1) starting at para. [0034]: The hybridoma is cultured to produce antibody.

Step 2) starting at para. [0037]: The hybridoma culture fluid is clarified with use of a 0.45 u filter.

Step 3) starting at para. [0042]: The clarified hybridoma culture fluid is then concentrated by ultrafiltration.

Step 4) starting at para. [0046]: The concentrate is then adsorbed to and eluted from a cation exchange column.

Step 5) starting at para. [0049]: The eluate from the cation exchange column is then further purified on a Protein A AFINI tea (sic. affinity) column.

Step 6) starting at para. [0052]: The eluate from the Protein A column is then concentrated by ultrafiltration.

Step 7) starting at para. [0056]: The ultrafiltered concentrate is then desalted by gel filtration on Sephadex G-25.

Step 8) starting at para. [0059]: The desalted concentrate is then added to an anion exchange column, such that the antibody is "does not stick to an anion exchanger" and such the monoclonal antibody is able "to make a column bypass" (i.e. flow –through the column), while impurities such as Protein A and complexes antibody-Protein A "stick".

Step 9) starting at para. [0064]: The flow through from the anion exchange column is then concentrated by ultrafiltration.

Further steps then prepare the concentrated antibody as a pharmaceutical.

Steps 5) and 8) of '194 correspond to steps 1) and 2) of instant claim 1. The presence of the intervening concentrating and desalting steps is certainly permitted by virtue of the facts that 1) the claim language is open to include such steps, and 2) applicant has exemplified at least one such intermediate step in section 2.1 of the specification. Applicant is referred especially to para. [0027]-[0031] and [0055]-[0058] of '194 for a disclosure of the nature of anion exchange materials and conditions.

The '194 reference does not teach the removal of aggregated antibody, after the anion exchange step. However, Racher et al teach that some monoclonal antibodies tend to aggregate during cell culturing or during purification, and they teach that a further step, after Protein-A and anion exchange chromatography, may be necessary to remove the aggregates. They suggest a further step of size exclusion chromatography, following anion exchange chromatography; see para. spanning pp 267-268 and first full para. of p 268. It thus would have been obvious that, for cases in which a particular monoclonal antibody tends to aggregate during cell culturing or during purification, to use the further step of size exclusion chromatography (SEC), following anion exchange chromatography, as taught by Racher et al. While there may be no verbatim teaching in the '194 reference that would lead one to consider Racher et al, it is considered that the reverse applies. That is, Racher et al give one the motivation to consider the further purification step of size exclusion chromatography (SEC), should a particular monoclonal antibody tend to aggregate during cell culturing/ purification. It is not necessary that the '194 reference mention aggregates at all (perhaps the exemplified antibody was one that did not aggregate, or perhaps the inventors overlooked the problem of aggregation?). Nevertheless, one of ordinary skill would certainly have wanted to consider the problem of potential aggregation, for the reasons set forth by Racher et al (para. spanning pp 267-268), and to address the problem should it exist.

From the above claims 1 and 8-10 would have been obvious.

Regarding claims 2-5, the '194 reference does not mention what the characteristics of the protein-A matrix designated as Religen IPA-400 may be (see para.

[0049]). However, the fact that this was provided by Repligen is taken as indicative that this had an engineered protein-A having the same characteristics as the engineered protein-A taught in EP 0,284,268 (cited on PTO-892), which is assigned to The Repligen Corp.

Regarding claim 6, note para. [0069] teaches that the antibody preparation, after ion exchange chromatography, had 1 mg antibody and 0.03 ng of protein-A.

Regarding claims 11-12, the '194 reference does not mention the addition of protease inhibitors in any of the exemplified steps.

Independent claim 13 is rejected with the consideration that step 8) of '194 corresponds to step 1) of instant claim 13, with the consideration that the term "fractionating" is to be broadly interpreted as encompassing a further fractionating of a single flow-through peak from the anion exchanger by an additional method, such as by size exclusion chromatography, as taught by Racher et al.

Regarding claim 21, the "collecting at least 70% of the amount of antibody loaded onto the anion exchanger" limitation is met by the reference, which discloses that there were 4.31 g of antibody at the end of step 5) (para. [0051]) and 4.31 g of antibody at the end of step 8) (para. [0063]). In other words, 100% of the amount of antibody loaded onto the anion exchanger was recovered.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over xx as applied to claims 1-3, 12 and 15-16 above, and further in view of Wan et al (6,177,548, cited on PTO-892).

Wan et al show a process for separating antibody monomers from aggregates. This process involves a flow-through mode of operation in which antibody monomers flow through an anion exchange column, while aggregates bind to the column. Wan et al teach that the pH of the loaded antibody preparation should be within +/- 0.2 pH units of the pI of the monomer product being purified. They teach that, at such a pH, the monomers will have a low charge and hence flow through the column, while aggregates will have a greater charge and hence bind to the anion exchange material in the column. See col. 1, lines 42-67. The pH range of +/- 0.2 pH units around the pI taught

by Wan et al is within the pH range of +/- 0.5 pH units around the pI that is recited in instant claim 17.

ART OF INTEREST

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Laursen et al (6,281,336, cited on PTO-892) show a process for separating antibody monomers from aggregates, by the sequential use of anion and cation exchange chromatography. This process involves the flow-through mode of operation monomers with the anion exchange column. There is no suggestion to divide the flow-through peak into fractions, particularly because Laursen et al teach that the anion exchanger should be preferably coupled in series to the cation exchange column. See col. 6, line 44-col. 7, line 26.

Ansaldi et al (6,620,918, cited on PTO-892) show the separation of protein monomers from aggregates. This process involves a bind-elute mode of operation using either cation or anion exchange chromatography.

Liu et al (2008/0058507, cited on PTO-892) show a process for separating antibody monomers from aggregates. This process involves a bind-elute mode of operation using anion exchange chromatography.

CONTACTS

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, whose telephone number is 571-272-0849. The examiner can normally be reached on Mon.-Thu. from 8:00 am to 5:30 pm and on alternate Fridays. The examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application is assigned is 571-273-8300.

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Typed 5/25/09 DAS

/David A Saunders/

Primary Examiner, Art Unit 1644